



## Potential of *Juniperus communis* L as a nutraceutical in human and veterinary medicine



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### ABSTRACT

Plants have been used for thousands of years as medicine for treating variety of diseases and medical complaints by most of the civilizations. *Juniperus communis* L. is an evergreen aromatic shrub with high therapeutic potential for the treatment of diseases in human and animals. The plant is rich in aromatic oils, invert sugars, resins, catechin, organic acid, terpenic acids, leucoanthocyanidin, alkaloids, flavonoids, tannins, gums, lignins, wax, etc. Juniper berries or extract of the plant has traditionally been used as diuretic, anti-arthritis, anti-diabetes, anti-septic as well as for the treatment of gastrointestinal and autoimmune disorders. The essential oil and extracts of juniper have been experimentally documented to have antioxidant, antibacterial, antiviral and antifungal activities. Recent studies have also found anti-inflammatory, cytotoxic, hypoglycemic and hypolipidemic effects of berries in experimental models. Further, the essential oil incorporation retarded lipid peroxidation in preserved meat due to its high antioxidant effect which not only improved meat product quality but also improved shelf life of the product. Thus natural antioxidant such as juniper can be used in place synthetic antioxidant for the preservation and improving self-life of meat products. New well designed clinical trials in human and animals using well-characterized *J. communis* extract or oil need to be conducted so that additional information is generated which can support the use of this natural product as a nutraceutical.

### 1. Introduction

The genus *Juniperus* (Family Cupressaceae) is evergreen aromatic shrub or tree mostly distributed throughout the cold and temperate regions of Northern Hemisphere with some species extending as far South as Tropical Africa. The genus consists of approximately 75 species depending on taxonomic features although taxonomists disagree on the exact number (Farjon, 2001; Adams, 2001). The widely known and perhaps most useful species is *Juniperus communis* L. commonly known as juniper, has the largest range of distribution than any woody plant extending from the Arctic regions of Asia, Europe and North America south to approximately 30° N latitude, although some studies have also reported that natural populations also occur in the Southern Hemisphere (Adams, 2004). In Asia, the plant grows naturally in the Himalayas and is found at an altitude of 3000–4000 m from Afghanistan to South-west China. Other common important *Juniperus* species of the Himalayan range include *J. indica*, *J. recurva* and *J. squamata* (Adams, 1987; Farjon, 2013).

*J. communis* a small coniferous evergreen tree or shrub variable in form ranging from 10 m tall to a low, often prostrate spreading shrub in exposed locations. It has green needle-like leaves in whorls of three with a single white stomatal band on the inner surface. It is dioecious with male and female cones which are wind pollinated on separate plants. The fruits are berry-like cones initially green which ripen in 18 months to purple-black with a blue wax coating. These berries are spherical 4–12 mm in diameters and usually have three (occasionally six) fleshy fused scales, each scale with a single seed. The seeds are dispersed when birds eat the cones digesting the fleshy scale and passing the hard seeds in their droppings. The male cones are yellow 2–3 mm in length and fall soon after shedding their pollen (Adams, 2004).

The astringent blue-black seed commonly are too bitter to eat raw and are dried for its use as a culinary component in different regions of the world. The dried berries are crushed or grounded to release their flavor before these are added to a dish. These are used to flavor meat, soups, sauces, stews, stuffing and pickled foods. The berries are also used to flavor certain alcoholic beverages like beer and gin. The essential oil

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extracted from ripe dried berries is aromatic having light fruity fragrance which is psychologically uplifting during the periods of low energy anxiety and general weakness. The branches and berries of juniper are burnt in temples to purify air during religious ceremonies (Rezvani et al., 2009).

Plants have been used for thousands of years as medicines for treating a variety of different diseases and medical complaints by most of the civilizations. Being useful therapeutic agents in their own right, an understanding of these traditional medicines has provided new plant-derived drug leads to modern medicine. Natural products obtained from the plant kingdom either an extract or essential oil is complex mixtures containing hundreds of organic compounds having applicability in food and cosmetic industries besides therapeutic applications. The berries have long been used as medicine by many cultures. Western American tribes combined the berries of *J. communis* with *Berberis* root bark in an herbal tea. The berries are used in traditional Turkish medicine as diuretic, antiseptic and treating gastrointestinal problems (Baytop, 1999). The anti-inflammatory potential of juniper was empirically established and transmitted in the folk medicine of different countries throughout Europe (Mascolo et al., 1987; Tunon et al., 1995). The fruits of plant have been used traditionally for the treatment of a migraine, rheumatic arthritis and gout. Native Americans used *J. communis* berries as female contraceptive as well as an anorexigenic agent and in the treatment of diabetes (Tilford, 1997; McCabe et al., 2005).

In Romania, juniper fruits are traditionally used as infusion or tincture internally for diuretic and antiseptic effects and externally for various dermatitic conditions (Bojor, 2003). Fruits have antiseptic and styptic effect and have been used for the treatment of piles and infantile tuberculosis. Aerial parts were used for acute and chronic cystitis, albuminuria, catarrh of the bladder, renal suppression, leucorrhoea and amenorrhoea. Bark of the plant has also been used in nephritic dropsy of children, asthma, gonorrhoea, pulmonary blennorrhoea, arthritis, respiratory affections, diabetes, bladder affections, chronic pyelophritis, cough, abdominal disorders and skin diseases. The whole plant has been used as anti-inflammatory, urinary antiseptic, diuretic, emmenagogue, sudorific, carminative and digestive disorders (Pepeljnjak et al., 2005; Gumral et al., 2013; Banerjee et al., 2013).

Recent experimental studies have demonstrated various pharmacological activities of essential oil and extract of juniper viz. antioxidant, antimicrobials, hypoglycemic, hypolipidemic, cytotoxic and anti-inflammatory. Other beneficial health effects reported for juniper includes hepatoprotective, neuroprotective, anti-fertility and renal effects. The supplementation of berries or their essential oil experimentally has been observed to have a positive impact on performance and yield in quails and such supplementation has been found to be a better alternative for synthetic antioxidants for the preservation of meat. However, human and veterinary clinical data substantiating such beneficial therapeutic effects are lacking. The review describes the chemical constituents, pharmacological activities and medicinal benefits of the *Juniperus communis* L. plant. Various scientific studies (*in vivo*, *in vitro* and clinical studies) have been included to validate different pharmacological activities of the plant which will justify its possible medical use in human and veterinary medicine.

## 2. Materials and methods

Literature available for the comprehensive study were taken from different worldwide accepted scientific database Science Direct (<http://www.sciencedirect.com>), PubMed (<http://ncbinih.gov/pubmed>), Springerlink (<http://www.springer.co.in>), Google Scholar (<http://www.onlinelibrary.wiley.com>) and abstracts, journals account for botanical description, pharmacological properties and ethno-botanical uses of different parts of *J. communis*. Text words and controlled vocabulary were devised by the authors for search strategy during the process of literature survey. No hold bars were imposed in terms of author(s) or type of publication during the literature survey. The

review highlights the botanical description, traditional uses, phytochemical constituents present in different part of *J. communis* and their pharmacological properties in a comprehensive manner.

*J. communis* plant is not only a rich source of nutrition but also is rich in aromatic oils and their concentration varies in different parts of the plant (berries, leaves, aerial parts, and root). The fruit berries contain essential oil (0.5% in fresh and 2.5% in dry fruit) invert sugars (15–30%), resin (10%), catechin (3–5%), organic acid, terpenic acids, leucoanthocyanidin besides bitter compound (Juniperine), flavonoids, tannins, gums, lignins, wax, etc (Koc, 2002; Martin et al., 2006; Senegül et al., 2008). Various flavonoids like biflavonoids (amentoflavone), flavones (apigenin), flavonols (quercetin, isoquercetin) and vitamins (vitamin C) have also been found to be present in juniper berries.

Phytochemical profiling of *J. communis* berry essential oils has mainly focused on the terpenoid content. The main terpenoids of essential oils are hydrocarbons of monoterpenes, sesquiterpenes and diterpenes whereas their oxygenated derivatives are only minor constituents (Ochocka et al., 1997; Höferl et al., 2014). The mono-terpenoids of berry essential oil amounted to 83% of which 69.4 % was found to be monoterpene hydrocarbons. The main monoterpene hydrocarbons were  $\alpha$ -pinene,  $\beta$ -pinene,  $\beta$ -myrcene sabinene, limonene whereas oxygenated monoterpene hydrocarbons include terpinen-4-ol, myretenol,  $\beta$ -citronellol, linalool, camphene hydrate, borneol, etc (Sela et al., 2011). Despite the domination of monoterpene compounds in the oils, there are differences in their quantitative composition due to a number of factors like geographical location, degree of ripeness, the age of berry fruit, production method, etc. Such variability in the composition of juniper essential oils was reported for the oils originated from different regions in Europe and America. The main constituents were pinenes, mostly  $\alpha$ -pinene varying in the juniper oil at different locations; 27% in the samples from Greece (Chatzopoulou and Katsiotis, 1993); 28.6–38.2% in Montenegro (Damjanović et al., 2006) and 46.6% in the samples from Iran (Rezvani et al., 2009).

Similarly, sesquiterpenes accounted for about 13.4% of the total berry oil and these are found to be both sesquiterpenes hydrocarbons and oxygen-containing sesquiterpenes. The major sesquiterpenes hydrocarbons present in the berry essential oil are germacrene B and D,  $\alpha$ - and  $\beta$ -selinene,  $\alpha$ -humulene, epi- $\alpha$ -bisabolol,  $\alpha$ -muurolene,  $\beta$ - and  $\delta$ -elemene whereas oxygenated sesquiterpenes included  $\alpha$ -cadinol, spathulenol, eudesmol, viridiflorol, germacrene D-4-ol, caryophyllene oxide, etc (Sela et al., 2011).

Bicyclic diterpenes in berries essential oil included imbricatolic acid, junicedral, trans-communic acid, iso-cupressic acid, arylteralin and lignin (Pascual et al., 1980; Chatzopoulou and Katsiotis, 1993). Three new diterpenes acids namely 15-dien-18-oic acid, 7-oxo-13-epi-pimara-8-oic acid 15-dien-18-oic acid, 7-oxo-13-epi-pimara-8-oic acid, 7 $\alpha$ -hydroxy-sandaracopimaric acid have also reported to be present in fruit berries essential oil (Gordien et al., 2009).

The presence of high amounts of other important components such as sabinene, germacrene D, myrcene,  $\beta$ -pinene and limonene in juniper oil have also been reported (Pepeljnjak et al., 2005; Orav et al., 2010). Similarly, essential oils from needle and wood were found to have high proportion of sesquiterpenes especially those bearing a tricyclic skeleton (cedrane and longifolane) whereas monoterpenes were present at very low amounts (Gonny et al., 2006).

## 3. Discussion

### 3.1. Antioxidant activity

Juniper fruit extracts have a strong antioxidant activity which stands established using different antioxidant assays which include *in-vitro* scavenging assays and metal chelating potential. The extracts (aqueous and ethanolic) exhibited a strong total antioxidant activity at the concentrations of 20, 40 and 60  $\mu$ g/ml. At these concentrations, both extracts of juniper fruit possess effective reducing power, metal chelating activity

as well as scavenging power in various scavenging assays (Elmastas et al., 2006). These fruit extracts were equipotent in inhibiting the peroxidation of the linoleic acid emulsion. Antioxidant activity of essential oils from the berries of different juniper species has also been established (Emami et al., 2007). *In-vitro* antioxidant capacity of essential oil of juniper using different radical scavenging assays and xanthine oxidase inhibitory effect was observed and such antioxidant activity of the oil was mainly attributable to electron transfer and not hydrogen atom transfer which make the juniper berry essential oil as a strong antioxidant. The possible blocking of oxidation process in living models has also been confirmed due to increased activities of various antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase (Höferl et al., 2014). The inhibition of the lipid peroxidation by the essential oil of juniper at both the stages (hydroperoxides and malondialdehyde formation) was less efficient than the inhibition of butylated hydroxylated toluene (Höferl et al., 2014). Such protective effect of *J. communis* essential oil on lipid peroxidation has also been corroborated by Stoilova et al. (2014).

The anti-radical activity depends on chemical nature and concentration of various components of oil (Wei and Shibamoto, 2007; Misharina et al., 2009). Terpenes hydrocarbons are preponderant regardless of the difference in the composition in the essential oil of juniper berries. In many cases the antioxidant activity of the oil is not exclusively attributed to  $\alpha$ - and  $\beta$ -pinene as these monoterpenes hydrocarbons don't contribute significantly to inhibit malondialdehyde formation (Wei and Shibamoto, 2007). It is rather  $\alpha$ - and  $\beta$ -terpinenes and to a lesser extent sesquiterpenes analogues that reduce cellular damage by inhibiting peroxidation of lipids. This stands established both for juniper essential oil (Misharina et al., 2009) and for pure terpene hydrocarbons, terpenolene,  $\alpha$ -terpinene and  $\gamma$ -terpinene, myrcene, as well as  $\alpha$ - and  $\beta$ -pinene which inhibit lipid peroxidation in later stages (Ruberto and Baratta, 2000). However, sabinene, limonene,  $\alpha$ - and  $\beta$ -pinene and myrcene show antiradical activity in relation to 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals (Roberto et al., 2010). The scavenging effect of hydroxy radical ( $\text{OH}^\cdot$ ) is due to  $\beta$ -pinene and limonene (Emami et al., 2007) whereas germacrene has a neutralization effect on superoxide radicals (Karioti et al., 2004). Various studies have observed that the monoterpenes content of essential oil enhanced antioxidant activity thereby imparting resistance in living organism against oxidative stress. The anti-radical activity affects the levels of most of the important enzymes viz. SOD, CAT, GPx and GST responsible for neutralization of reactive oxygen and nitrogen species (Van Lieshout et al., 1998; Roberto et al., 2010).

Polyphenols and polyphenol esters in addition to monoterpene hydrocarbons have also been isolated from the fruit of *J. communis* (Ochocka et al., 1997). The hydroxyl group present in the phenolic compounds is primarily responsible for the antioxidant effects (Shahidi et al., 1992). The total phenol contents have also been reported to be high in the ethyl acetate extract fraction of juniper leaves (Ved et al., 2017). Polyphenolic compounds present in juniper extracts have also been shown to have significant antioxidant activity against various *in-vitro* antioxidant systems. These components in the extracts have shown significant antioxidant activity due to strong hydrogen donating and metal chelating properties and their effectiveness as scavengers of hydrogen peroxide, superoxide and other free radicals. Therefore, juniper fruit can be used as an easily and accessible source of natural antioxidant.

### 3.2. Neuroprotective effects

The extracts of *J. communis* had shown protective effect on nervous tissue and enhance working memory in exposed animals. Therefore, it can be a potential alternative treatment for Parkinson, Alzheimer and other chronic neurological disorders. It has been reported that methanolic extract possessed a therapeutic effect in reserpine-induced Parkinson disease animal model (Bais et al., 2014a,b). Similarly, the plant extract was also reported to possess significant neuroprotective effect against chlorpromazine-induced Parkinson like symptoms (Rana and Bais, 2014). The inhalation of volatile oil at the rate of 1% or 3% daily for

21 days improved amyloid- $\beta$  induced memory deficits in rat model of Alzheimer disease (Cioanca et al., 2015). The inhalation of volatile oils was found to inhibit Acetylcholinesterase (AChE) activity and prevent oxidative damage in brain of rodents in a dose dependent manner (Cioanca et al., 2015) due to its significant antioxidant potential and ability to inhibit AChE activity involved in the progression of neurological disorders.

### 3.3. Antidiabetic effects

Juniper berries decoction orally administered to normal healthy rats induced significant hypoglycemia. Daily administrations of decoction for 24 days produced significant hypoglycemia in streptozotocin-induced diabetic rats (Sanchez et al., 1994). This effect could be due to the improved peripheral utilization of glucose due to high insulin-like activity of decoction and/or its ability to heal pancreas particularly when there is no permanent damage. Similarly, administration of ethanolic extract of juniper berries also displayed a hypoglycemic effect in diabetic rats (Orhan et al., 2012). The ethanolic extract of Chinese juniper berries has also been reported to possess a potential hypoglycemic effect whereas the aqueous extract had a potential hypolipidemic effect in alloxan-induced diabetic rats (Ju et al., 2008). The methanolic extract produced a dose-dependent and significant reduction not only in blood glucose level but also total cholesterol, triglycerides, low-density lipoproteins (LDL), Very low-density lipoproteins (VLDL) with the elevation of high-density lipoproteins (HDL) levels in diabetic rats (Banerjee et al., 2013). The administration of essential oil of juniper significantly decreased cholesterol, triglycerides and oxidized LDL and other associated changes in hypercholesteromic rats (Akdogan et al., 2012).

### 3.4. Hepatoprotective effects

The hepatoprotective activity of *J. communis* was determined in carbon tetrachloride-induced hepatotoxic model. Administration of ethanolic or aqueous extracts of *J. communis* berries reduced the elevated serum levels of hepatic damage biomarkers viz. aspartate and alanine aminotransferase, alkaline phosphatase and bilirubin (Manvi and Garg, 2010). The ethyl acetate fraction of juniper leaves was investigated for its hepatoprotective effect in paracetamol induced hepatic damage in rats. This fraction treated hepatotoxic rats exhibited remarkably decrease in the elevated levels of serum aspartate and alanine aminotransferase, alkaline phosphatase and direct bilirubin as compared to untreated hepatotoxic rats (Ved et al., 2017). Ethanolic fruit extract of *Solanum xanthocarum* along with *J. communis* daily for 14 days significantly attenuated the liver toxicity induced by co-administration of paracetamol and azithromycin. The prolonged treatment not only normalized the biochemical markers but also reversed the histopathological changes in the hepatic tissue of rats (Singh et al., 2015).

### 3.5. Antibacterial effect

Several studies have reported growth inhibitory activity of essential oil obtained from berries toward multiple bacterial species (Filipowicz et al., 2003; Pepeljnjak et al., 2005). The inhibitory activity of *J. communis* essential oil against *Bacillus cereus*; *Escherichia coli*; *Listeria monocytogenes*; *Corynebacterium species* and *Staphylococcus aureus* has been evaluated. Of the bacterial species tested the growth of *Staphylococcus aureus* and *Escherichia coli* was significantly inhibited (Glisic et al., 2007). The essential oil on the basis of minimum inhibitory concentration (MIC) was reported to have highest microbial activity against *Staphylococcus aureus* and *Streptococcus pyogenes* and moderate activity against *Streptococcus agalactiae*, *Hemophilus influenzae*, *Corynebacterium species* and *Campylobacterium species* and *Campylobacter jejuni*. The bacteria which were completely resistant to antimicrobial activity of Juniper oil included *Staphylococcus epidermidis*, *Salmonella enteritidis*, *Shigella flexneri*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus*

*aeruginosa*, *Proteus mirabilis* and *Actinobacter spp.* *J. communis* essential oil at a concentration of 20 and 50 % was also reported to possess antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (Rezvani et al., 2009). The essential oil of *J. communis* growing wild in Estem Kosova was found to have moderate to high activities against *Staphylococcus aureus*, *Escherichia coli*, *Hafina alvei* with the zone of inhibition 10–35 mm for the concentration of 5 mg/ml. However, *Pseudomonas aeruginosa* was resistant to the inhibitory activity of the essential oil (Haziri et al., 2013). Conversely essential oils and their major compounds of the *Juniper communis spp communis* were reported to possess non-significant inhibitory effect against *Staphylococcus aureus*, *Escherichia coli* and *Staphylococcus aureus* (Angioni et al., 2003). The polar *J. communis* with MIC values less than 1000 µg/ml i.e. 10 µg impregnated on the disc (Fernandez and Edwin, 2016). All the organic crude leaf extracts (methanol, ethanol, ethanol, hexane and chloroform) except aqueous extract have been reported to possess a good antibacterial activity against five pathogenic multidrug-resistant bacteria viz. *Bacillus subtilis*, *Escherichia coli*, *Agrobacterium chrysanthemi*, *Erwinia chrysanthemi* and *Xanthomonas phaseoli*. On the basis of the zone of inhibition hexane extract displayed maximum inhibition against the test organisms followed by ethanol, methanol and chloroform extract, respectively. The inhibitory activity of these extracts on the basis of MIC was found to be more as compared to standard antibiotics like ampicillin (10 mcg) and erythromycin (15 mcg) which were used as positive control (Sati and Joshi, 2010).

The active constituents isolated from an n-hexane extract of *J. communis* roots as well as aerial part displayed anti-mycobacterium activity and such activity was attributed to sesquiterpenes identified as longifolene and two diterpenes namely totarol and transcommunic acid (Gordien et al., 2009). Similarly diterpenes - isocupressic acid, cumminic acid and arly tetralin ligan, deoxypodophyllotoxin, isolated from *J. communis* were tested as inhibitory agents for *Mycobacterium spp.* The isocupressic acid and cumminic acid displayed maximum activity against *M. tuberculosis* H37Rα with MIC of 78µM and 31µM whereas deoxy-podophyllotoxin was observed to be least effective with MIC of 1004 µM (Carpenter et al., 2012). Previous studies on phytochemical profiling of *J. communis* essential oils have focused on the terpenoids content (Glisic et al., 2007). A number of terpenes including α-pinene, sibeneine mycene, p-cymene, D-limonene, γ-terpinene, terpinolene, 1-terpinen-4-ol, β-caryophyllene, and bicyclo-germacrene were found to be present in significant levels in essential oils (Glisic et al., 2007). This study also identified the presence of a number of other minor terpenoids components such as α-cubelene, α-copaene α-humulene, germacrene-D, and γ-cadinene. Many of these terpenoids are known to have broad-spectrum antimicrobial activity and may be contributing to the growth inhibitory activity of the oil on pathogenic bacteria reported in various studies. Various junipers extracts like methanolic, aqueous and ether having potent or moderate growth inhibitory activities, were found to have high levels of phenolic compounds, alkaloids, flavonoids and tannins (Fernandez and Edwin, 2016). Many studies have reported potent antibacterial activities for a wide variety of flavonoids (Narayana et al., 2001). Similarly, a number of tannin compounds have bacterial growth inhibitory activity. Gallo-tannins have been reported of inhibiting the growth of wide spectrum of bacterial species through a variety of mechanisms including cell surface molecules (Hogg and Embery, 1982) and by inhibiting glucosyl-transferase enzymes (Wu-Yuan et al., 1988). Elligtannins have high inhibitory activity on bacterial growth and function via several mechanisms including interaction with cytoplasmic oxido-reductases and by disrupting bacterial cell wall (Hogg and Embery, 1982; Buzzini et al., 2008). It is also likely that other phytochemical constituents present in these extract may also contribute to bacterial growth inhibitory properties. Alkaloids, anthraquinones, flavonoids, polyphenols, phytosterols and saponins present in various plant species have also been linked to antibacterial activity. Therefore, these phytochemicals present in *J. communis* berry extract or essential oil may be contributing to the bacterial growth inhibition.

### 3.6. Antifungal activity

Fractions, as well as essential oil of juniper, have inhibitory activity on yeast and certain fungi. Juniper leaf extracts in organic solvents (chloroform, methanol, ethanol and petroleum ether) were screened against aflatoxigenic *Aspergillus flavus* and it was found that methanolic extract caused maximum percent growth inhibition followed by ethanol (52%), petroleum ether (39%) and chloroform (27%) at 400 ppm concentration (Kumar et al., 2010). The hydro-alcoholic fruit extract of *J. communis* was also reported to be effective as antifungal against *Aspergillus niger* and *Penicillium hirsutum* and such activity can be correlated with its phytochemical contents mainly polyphenols (Fierascu et al., 2018).

### 3.7. Anti-fertility effects

The extract of *J. communis* has an anti-fertility effect due to its anti-progestagenic activity (Pathak et al., 1990). The hydro-alcoholic extract of fruits of *J. communis* was reported to possess dose-dependent anti-implantation activity when it was administered at the rate of 300 and 500 mg/kg body weight orally from day 1–7 of pregnancy (Agrawal et al., 1980). Further, it had abortifacient activity at both dose levels when administered on day 14, 15, 16 of pregnancy. There have been no reports of teratogenicity associated with the administration of extract to pregnant animals (Agrawal et al., 1980).

### 3.8. Gastrointestinal effects

Juniper has been reported to be useful in alleviating various gastrointestinal disorders due to its digestive, carminative, anti-spasmodic and anti-bacterial action (Pepejnjak et al., 2005; Banerjee et al., 2013; Gumral et al., 2013). The berries being bitter in nature have digestive action. Chewing of berries is useful to treat inflamed and infected gums due to its antiseptic and anti-inflammatory effect. Leaf extract has also been reported to have antiulcer properties. The intra-peritoneal administration of crude extract at a dose of 50 and 100 mg/kg has been reported to significantly inhibit aspirin, serotonin, indomethacin, alcohol or stress-induced gastric ulceration in rats and histamine-induced duodenal ulcers in guinea pigs. The leaf extract significantly enhanced the healing rate of induced ulcer in rats. The extract was found to significantly decrease volume and total acid of gastric juice without altering the pH and peptic activity (Pramanik et al., 2007). The anti-spasmodic effect of juniper is due to anti-inflammatory, analgesic and carminative action.

### 3.9. Anti-inflammatory activity

The anti-inflammatory activity of extracts of juniper plant native to different regions of the world has been reported. Depending on the plant material and solvent used for the extraction different researchers have reported the anti-inflammatory potential of the plant ranging from average to very good. Scientific evidence of an anti-inflammatory effect of *Juniperus taxa* is provided by many *in-vitro* and *in-vivo* studies. Mascolo et al. (1987) evaluated the hydroalcoholic extracts of most frequently used plants of Italian folk medicine for *in-vivo* anti-inflammatory activity using carrageenin foot oedema model and found *J. communis* was among the first four species for such activities. Anti-inflammatory activity of *J. communis* fruit was determined using isolated cells for assays of prostaglandin biosynthesis and platelet activating factor (PAF) induced exocytosis. The aqueous extract of juniper has showing 55% prostaglandin inhibition and 78% platelet activating factor-induced exocytosis inhibition (Tunon et al., 1995). Evaluation of five Turkish *Juniperus taxa* methanolic and aqueous extracts for anti-inflammatory activity in carrageenin and prostaglandin-induced hind paw oedema revealed a good anti-inflammatory activity which offered scientific support for its such traditional use (Akkol et al., 2009). However, Kalinkevich et al.

(2014) found the average anti-inflammatory potential of ethanolic extract of *J. communis* native to Russia. Fierascu et al. (2018) also reported anti-inflammatory activity after administering micro-emulsion of a hydro-alcoholic extract of juniper berries native to Romanian Southern Sub-Carpathian hills. The micro-emulsion was observed to decrease the paw edema in dextran-induced inflammation model indicating anti-histaminic and anti-serotonin properties of juniper. However, in kaolin-induced inflammation model, the anti-inflammatory effect of juniper was due to down-regulation of pro-inflammatory cytokines viz. IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . The juniper micro-emulsion was found to be rich in phenolic compounds including flavonoids which may be responsible for down-regulation of pro-inflammatory cytokines as studies have shown that flavonoids down-regulate inflammatory cytokines expression (Jajtner et al., 2016; Zeinali et al., 2017).

The anti-arthritis effect of amentoflavone isolated from *J. communis* has been studied against Freud's adjuvant-induced arthritis. At the dose of 40 mg/kg, amentoflavone was found to possess potential useful anti-arthritis activity as it controls inflammation in an adjuvant-induced experimental model (Bais et al., 2016). The extract is rich in mono-terpenoids including limnane and  $\alpha$ -pinene which have the ability to suppress the NF- $\kappa$ B signaling pathway which is a major regulator of inflammatory disease (Salminen et al., 2008).  $\alpha$ -Pinene affects inflammation by inhibiting P<sup>65</sup> translocation in the lipopolysaccharide induced nuclear factor signaling (Zhou et al., 2004). Furthermore many other sesquiterpenes and sesquiterpenes lactones present in juniper have also well established anti-inflammatory activities (Salminen et al., 2008). The mechanism(s) for anti-inflammatory activity has not been fully characterized but it appears that NF- $\kappa$ B inhibitory activity may be responsible for such activities. Thus the terpenes relieve symptoms of inflammation by down steaming the inflammatory stages of autoimmune inflammatory diseases.

### 3.10. Analgesic activity

Analgesic activity of methanolic extract of *J. communis* using different nociceptive tests in rodents has been reported (Banerjee et al., 2012). The extract was reported to have significant and dose-dependent analgesic activity which was blocked by naloxone thereby confirming the central analgesic activity of plant extract. Studies have revealed that  $\alpha$ -pinene, linalool and 1-octanol contribute to the topical anti-inflammatory and analgesic activities by inhibiting the activities of cyclooxygenase-2 (Li et al., 2016).

### 3.11. Anti-proliferative activity

In an initial study on an anti-proliferative activity, the aqueous *J. communis* berry extract was observed to have a significant inhibition in the growth of MCF-7/AZ mammary carcinoma cells (Van Slambrouck et al., 2007). Whilst this study did show significant inhibition of MCF-7/AZ cells following repeated exposure to extract but the inhibition was not greater than 50% at any tested dose. The highest dose (180  $\mu$ g/ml) used in this study inhibited cellular protein expression by approximately 90 percent. Such anti-proliferative effect of aqueous berry extract of juniper may be due to inhibition of growth rather than induction of apoptosis. The methanol and aqueous juniper berry extract also proved effective in blocking the proliferation of colorectal cancer cell line (Caco-2) and Hela cervical cancer growth with IC<sub>50</sub> values for Caco-2 and Hela carcinoma cells approximately 500  $\mu$ g/ml and 2000–2500  $\mu$ g/ml, respectively (Fernandez and Edwin, 2016). However, the test sample used was crude extract and it is possible that more than one anti-proliferative compound was present making the extract to function via pluripotent mechanisms. The juniper berry extract due to anti- and pro-oxidant capacities of the ingredients was reported to induce apoptosis in human neuroblastoma SH-SY5Y (Lantto et al., 2016). Similarly, the berry essential oil has been found to cause apoptosis in a drug-resistant strain of leukemia, HepG2 (liver cancer) cells and SH-SY5Y

(neuroblastoma) cells (Saab et al., 2012; Lantto et al., 2016). These effects of juniper berries may be due to the presence of phenolic compounds which affect the different cell signaling pathway inducing both cell cycle progression and apoptosis (Lantto et al., 2016). Various reported studies on cytotoxicity of *J. communis* or its active phytoconstituents are presented in Table 1.

### 3.12. Renal effects

Juniper plant is known as urinary antiseptic and diuretic among other effects in folk medicine. Few studies have also substantiated the claim of folk medicine of it being diuretic and urinary antiseptic. Continued daily administration of 10% aqueous infusion of juniper, 0.1% aqueous solution of juniper oil (with 0.2 % Tween 20 as solublizer) and 0.01% of terpinol-4-ol an active component of volatile oil in rats stimulate diuresis from day 2. Significant and prominent diuretic effect was only observed with 10% aqueous infusion of juniper suggesting that the diuretic effect is partially due to essential oil and partially due to hydrophilic constituents (Stanic et al., 1998). Juniper increases urine output without loss of electrolytes. The diuretic activity of aqueous infusion of juniper berries is attributed in terpinol-4-ol and to hydrophilic constituents which increase glomerular filtration rate. Moreover, terpinol-4-ol is also known to cause irritation to kidneys (Tisserand and Balacs, 1995) which may contribute to diuresis. However, excessive use of active ingredients or continue use may produce renal irritant effect particularly when the urinary tract is inflamed. Therefore, medicinal use of juniper is no longer recommended for treatment of various renal disorders particularly when the patients have underlying renal cause. Moreover, oral administration of lyophilized aqueous extract of juniper to rats at 1000 mg/kg body weight neither increased urine volume or excretion of sodium, potassium and chloride ions over a 6-h period compared to the effect of the same volume of water (Lasheras et al., 1986).

## 4. Conclusions

The nutraceuticals deals with any product derived from plant sources with extra health benefits in addition to the basic nutritional value in the foods. Antibiotic including ionophores use in livestock and poultry diet as a growth promoter has declined because of increasing residual concerns in human and animal health and emergence of resistance bacteria with potential risk to human health. Therefore, studies are being conducted to identify and develop new feed additive as an alternative to antibiotics and use of natural additives is being particularly preferred (Ozkan and Acikgoz, 2007). Herbs, aromatic plants or their extracts are considered as effective natural feed additives and are receiving increased attention as possible antibiotic growth promoter replacement (OJEU, 2003; Wallace et al., 2002; Adiyaman and Ayhan, 2010). The supplementation of essential oils obtained from various aromatic plants to livestock and poultry provide general benefits like increasing the flavor of feed, prevent toxin development, provide better nutrient use with increased digestive activity, improve animal performance, support immune system besides increasing the yield of the animal products with low cholesterol and free of residues (Yurtseven et al., 2008). Although there are limited studies about effects of essential oil of aromatic plants on poultry traits, many studies focused on positive impacts of such additives to poultry diets (Jamroz and Kamel, 2002; Wallace et al., 2002). In recent years, decreased feed intake and reduced mortality rates with improved feed conversion ratios (FCR) and carcass quality have been reported with the use of aromatic plants in broiler diets. Also, increased weight gain, a positive impact of digestive system and improved feed flavor were also reported with the addition of such aromatic plant additives to broiler diets (Ilcim et al., 1998; Lee et al., 2003). Studies on the incorporation of extract or essential oil of juniper berry have been evaluated on performance parameters in poultry. Lewis et al. (2003) indicated significantly improved feed conversion ratio with juniper berry supplementation in broiler diets. Similarly, juniper berries supplementation in low levels (0.5

**Table 1**  
*In-vitro* cytotoxicity of *J. communis* L or Its Active Constituents in Experimental Models.

Fraction/Active constituent	Experimental model	Cytotoxic effect	Reference
Aqueous berry extract	MCF-7/AZ mammary carcinoma cells	The anti-proliferative effect due to inhibition of cellular receptor tyrosine kinases, insulin-like growth factor receptors (IGF-1R) and C-erbB2/HER2/neu receptors	Van Slambrouck et al. (2007)
Berry extract	Human neuroblastoma SH-SY 5Y cells	Activated cellular relocalization of p53 and DNA fragmentation dependent cell death by induction of p53 associated apoptosis through the potentiation and synergism by several plant phenolics	Lantto et al. (2016)
Ethyl acetate fraction of <i>J. communis</i> leaves	Cell viability assay on HepG2 cells	Fraction in WST-1 proliferation assay didn't affect HepG2 cell viability after treatment for 24 h at a concentration between 0-10 µg/ml	Ved et al. (2017)
Extract of areal part of <i>J. communis</i>	In-vitro assay on Human prostate cancer cells (PC-3), Human colon cancer cells (HCT-116) and mammary cancer cells (MCF-7) using MTT	Highest activity with the safest margin observed for the total methanolic extract against human breast cancer cell line (MCF-7)	Ghaly et al. (2016)
Diterpenes isocupressic and aryltetralin lignan deoxydopodophyllotoxin from <i>J. communis</i>	Malignant – MB231 breast cancer cells	Induced caspase dependent programmed cell death (apoptosis); aryltetralin lignan deoxydopodophyllotoxin inhibited cell survival pathways mediated by the MAPK/ERK and NK-κβ signaling pathways within hours of treatment	Benzina et al. (2015)
Imbricaticolic acid isolated from methanolic extract of ripe berries	p <sup>53</sup> null CaLu-6 cells	Induced up-regulation of cyclic dependent kinase inhibitors and their accumulation in G1 phase of the cell cycle and also degradation of cyclines A, D1 and E	
Methanolic and aqueous berry extract	Colorectal cancer cell line CaCO <sub>2</sub> and HeLa cervical cancer cell line	Block the proliferation of cells in both cell lines with IC <sub>50</sub> between 500-2500 µg/ml	Fernandez and Edwin (2016)

and 1.0%) in the diets of quails had a positive impact and yields viz. live weight, feed intake and carcass traits. Similarly, juniper essential oil added at 100 and 150 mg/kg feed of quails daily for 42 days during growing and finishing periods induced a significant increase in live weight, live weight gain, and carcass yield. However, feed intake and feed conversion ration were not significantly influenced by such treatments (Yesilbag et al., 2014).

The major antioxidants used in wide range of food industries are synthetic in nature but due to potentially toxic and carcinogenic effects of these artificial antioxidants, their replacement with natural antioxidants is highly suggested (Parke and Lewis, 1992). Over the year's synthetic antioxidants such as hydroxyanisole, butylated hydroxytoluene and tertiary hydroquinone have been widely used to preserve meat and meat products (Fasseas et al., 2007). The use of these antioxidants has been questionable in view of their toxic, pathogenic and carcinogenic effects in human and animals (Hayes et al., 2011a,b). Therefore, there is a growing interest in the use of natural antioxidants. It has been reported that natural antioxidant especially those from plants have greater application potential in terms of consumer acceptability, palatability, stability and shelf life of meat products (Jung et al., 2010).

Natural antioxidants such as juniper oil have been used in place of synthetic antioxidants to retard lipid peroxidation in stored meat (Yesilbag et al., 2014). Such incorporation of oil is not only increased the shelf-life of stored meat but also improved the meat product quality. The juniper essential oil has also been used successfully in the production of cooked pork sausages with enhanced quality (Šojić et al., 2017). Scientific reports highlighting the potential for utilization of juniper essential oil or extracts for animal production and health are scarce in the literature.

Juniper is safe for most adults when taken orally in medicinal amount for short term or when inhaled as a vapor or when applied to skin in small areas. However, oral administration of juniper for a long time or in high doses can be unsafe and cause kidney problems and irritation of the gut. Juniper berries could affect the blood pressure and make its control more difficult. The consumption of berry extract of juniper might lower blood sugar too much in a patient with diabetes. Therefore, the berry extract should be avoided by patients taking medication for diabetes mellitus because it may cause a further decrease in blood sugar to very low levels. Few toxicological studies exist on juniper woods or their extracts (Gross and Ezerietis, 2003; Meding et al., 1996). *J. communis* wood has been tested for its use as an implant material in rabbits with concurrent toxicity studies following oral or intravenous administrations. It was found that a low concentration of oil that would be released from the

wood was tolerated without any detrimental effects (Gross and Ezerietis, 2003). An acute dermal LD<sub>50</sub> for juniper berry oil in rabbits has been >5 g/kg (Andersen, 2001). Oral gavage of common juniper needle extract was found to be abortifacient and affected the fertility in studies involving albino rats (Gardner et al., 1998). Therefore, it is unsafe to administered juniper extract in pregnant or in animals about to become pregnant. The essential oil can also prove to be toxic when ingested in higher doses due to strong irritant effect to intestines and kidneys which may result in diarrhea, stomach or kidney ache, haematuria or albuminuria and increase heart rate. The essential oil of juniper has not been found to sensitize skin or induce phototoxicity in animal tests. Therefore, the oil is safe for massage, inhalation, or for its use as an ingredients in various cosmetic formulations. However, the oil for external use needs to be diluted so that it does not produce irritations or blisters in the skin. The adverse reactions like dermatitis, nasal congestion or blisters, have been observed in sensitive or people allergic to juniper essential oil. Juniper oil based phytomedicine was tested for nephrotoxicity in sprague-dawley wistar rats following oral administration at varying dose and the oil was found to be free of nephrotoxicity. *J. oxycedrus* tar was found to be genotoxic in various genotoxicity assays. However, no such toxicity has been attributed to *J. communis* (Andersen, 2001).

Potential medicinal applications of berry or extract of *J. communis* in several traditional medical systems describes its use as a diuretic, general antiseptic as well as for treating gastrointestinal disorders. They are also used for the treatment of rheumatic arthritis and diabetes. Recent scientific papers describe variety of pharmacodynamic effects of juniper natural products. The essential oils and extracts of juniper have been experimentally documented to have antioxidant, antibacterial, antiviral and antifungal activities. The growth inhibitory activity of *J. communis* berry extract on the growth of bacteria associated with triggering autoimmune inflammatory diseases like rheumatic arthritis indicate its potential in the treatment and prevention of selected s potential in the treatment and prevention of selected autoimmune inflammatory diseases. Recent studies have also been determined anti-inflammatory, cytotoxic, hypoglycemic and hypolipidemic effects of berries of *J. communis* in experimental models. However, clinical data in humans substantiating such therapeutic effects are lacking in the literature.

Incorporation of juniper berry extract or essential oil in broiler or quails diets had positive effect on growth performance parameters and can replace synthetic antioxidant for preservation of meat. The data describing the use of juniper as a nutraceutical in animal production and health is lacking. Therefore, new well designed clinical trials in farm animals and poultry using well-characterized *J. communis* extract or oil

need to be conducted so that additional information is generated which can support the use of this natural product as a veterinary nutraceutical.

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